# The role of regulatory B cells in allergen immunotherapy

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Abstract: PURPOSE OF REVIEW Allergen immunotherapy (AIT) is currently the only curative treatment available for allergic diseases, and has been used in clinical practice for over a century. Induction and maintenance of immune tolerance to nonhazardous environmental and self-antigens is essential to maintain homeostasis and prevent chronic inflammation. Regulatory B (BREG) cells are immunoregulatory cells that protect against chronic inflammatory responses primarily through production of anti-inflammatory cytokines such as IL-10, transforming growth factor- , and IL-35. The importance of BREG cells has been extensively demonstrated in the context of autoimmune diseases. Data showing their role in the regulation of allergic responses are slowly accumulating. This review summarizes recent findings relevant to the topic of BREG cells and their potential role in AIT. RECENT FINDINGS BREG cells support AIT in models of allergic airway inflammation and intestinal inflammation through induction of regulatory T (TREG) cells. In humans BREG frequency increases during venom immunotherapy while the phenotype of allergen-specific B cells changes. Mechanisms of BREG-mediated tolerance to allergens include IL-10-mediated suppression of effector T cell, including TH2 responses, induction of TREG cells, IL-10-mediated inhibition of Dendritic cell maturation, modulation of T follicular helper responses, and production of anti-inflammatory IgG4 antibodies. SUMMARY Current evidence supports a potential role for BREG cells in induction and maintenance of allergen tolerance during AIT. A better understanding of the role of B cells and BREG cells in AIT could open potential new windows for developing targeted therapies specifically focused on promoting BREG responses during AIT.

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# The role of regulatory B cells in allergen immunotherapy

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Allergen immunotherapy (AIT) is currently the only curative treatment available for allergic diseases, and has been used in clinical practice for over a century. Induction and maintenance of immune tolerance to nonhazardous environmental and self-antigens is essential to maintain homeostasis and prevent chronic inflammation. Regulatory B ($B_{REG}$) cells are immunoregulatory cells that protect against chronic inflammatory responses primarily through production of anti-inflammatory cytokines such as IL-10, transforming growth factor-β, and IL-35. The importance of $B_{REG}$ cells has been extensively demonstrated in the context of autoimmune diseases. Data showing their role in the regulation of allergic responses are slowly accumulating. This review summarizes recent findings relevant to the topic of $B_{REG}$ cells and their potential role in AIT.

**Recent findings**
$B_{REG}$ cells support AIT in models of allergic airway inflammation and intestinal inflammation through induction of regulatory T ($T_{REG}$) cells. In humans $B_{REG}$ frequency increases during venom immunotherapy while the phenotype of allergen-specific B cells changes. Mechanisms of $B_{REG}$-mediated tolerance to allergens include IL-10-mediated suppression of effector T cell, including $T_H2$ responses, induction of $T_{REG}$ cells, IL-10-mediated inhibition of Dendritic cell maturation, modulation of T follicular helper responses, and production of anti-inflammatory IgG4 antibodies.

**Summary**
Current evidence supports a potential role for $B_{REG}$ cells in induction and maintenance of allergen tolerance during AIT. A better understanding of the role of B cells and $B_{REG}$ cells in AIT could open potential new windows for developing targeted therapies specifically focused on promoting $B_{REG}$ responses during AIT.

**Keywords**
allergen immunotherapy, allergy, regulatory B, IL-10, tolerance

## INTRODUCTION

Allergen immunotherapy (AIT) has been used as a curative treatment for allergies for more than a century and many of its underlying mechanisms have been elucidated. These include early desensitization of mast cells and basophils, induction of Regulatory T ($T_{REG}$) cells, production of allergen-specific IgG (particularly IgG4) antibodies, suppression of eosinophil activation and migration [1,2]. In addition, several recent studies suggest a potential role for regulatory B ($B_{REG}$) cells in AIT [3].

## PHENOTYPE AND FUNCTION OF REGULATORY B CELLS

$B_{REG}$ cells exhibit anti-inflammatory functions, and their immunosuppressive role has been demonstrated to varying degrees in autoimmune disease, cancer, transplantation, infection, and allergic inflammation [3,4].

## SUPPRESSIVE MECHANISMS OF REGULATORY B CELLS

$B_{REG}$ cells act primarily through secretion of the immune-modulatory cytokines [3]. Most studies have focused on the role of IL-10 as the key factor through which $B_{REG}$ cells modulate immune responses and protect against excessive inflammation [5–10]. IL-10 has a wide range of suppressive effects on different cells types and has been widely recognized as an immune tolerance-inducing factor

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## KEY POINTS

- Current evidence supports a potential role for $B_{REG}$ cells in induction and maintenance of allergen tolerance.
- IL-10-producing $B_{REG}$ cells expand during AIT in murine models of allergic airway and intestinal inflammation, as well as in human VIT.
- $B_{REG}$ cells may contribute to tolerance induction during AIT include IL-10-mediated suppression of effector T cell, including $T_H2$ responses, induction of $T_{REG}$ cells, IL-10-mediated inhibition of DC maturation, modulation of $T_{FH}$ responses, and production of anti-inflammatory IgG4 antibodies.

in patients with different chronic inflammatory diseases [11]. Transforming growth factor-β (TGF-β) has also been identified as $B_{REG}$-associated suppressor molecule. TGF-β is involved in many processes including tissue remodelling and immune regulation. An important role for TGF-β in the context of immune tolerance is its capacity to support conversion of naive $CD4^+$ T cells to $T_{REG}$ cells [11]. Finally, IL-35 has also been linked to $B_{REG}$-mediated immune suppression [12]. IL-35 can promote immune tolerance through induction of $T_{REG}$ proliferation and suppression of $T_H17$ responses [11].

Apart from secreted cytokines, other molecules have been associated with $B_{REG}$-mediated suppressive effects. These include the membrane-associated molecules such as CD19 [13], CD62L and MHC-II [14], fas ligand [15], T-cell immunoglobulin and mucin domain [16], and programmed death ligand 1 [8,17–20], as well as the intracellular signalling molecules signal transducer and activator of transcription 3 and myeloid differentiation response gene 88 [21].

In the context of human allergen tolerance induction, the production of IgG4 antibodies deserves some attention. IgG4 is considered to compete with IgE for allergen binding and therefore may function as a blocking antibody. Some unique features of IgG4 such as antigen-binding fragment-arm exchange, its low affinity for activating fragment crystallizable receptors, and its inability to fix complement render IgG4 an anti-inflammatory immunoglobulin isotype [22,23].

One of the mechanisms through which $B_{REG}$ cells could play a role in AIT, is through the modulation of T-cell responses. $B_{REG}$ cells have been shown to induce $T_{REG}$ cells in several different models [3,24,25]. Apart from induction of $T_{REG}$ cells, $B_{REG}$ cells could support AIT through suppression of effect T-cell proliferation and cytokine production [8,26]. A recent study provided compelling data demonstrating that $B_{REG}$ cells could modulate T follicular helper ($T_{FH}$) cell responses. Cocultures of in-vitro generated human $T_{FH}$ cells with B cells resulted (as expected) in plasma cell and memory cell differentiation. Upon addition of B cells that were stimulated for 3 days with CD40L and TLR9-ligand CpG2006 (these cells were considered $B_{REG}$ in this study), the B-cell differentiation was inhibited, and forkhead box (FoxP)$3^+$C-X-C chemokine receptor (CXCR)$5^+$ programmed death ligand-$1^+$ regulatory $T_{FH}$ were expanded. CD40, CD80, CD86, as well as IL-10 and TGF-β played a role in this process. These findings suggest that $B_{REG}$ cells can interfere with germinal centre reactions through modulation of $T_{FH}$ cells [27▪]. A weakness in this study is the fact that stimulated total B cells were used as $B_{REG}$, whereas only a fraction of these cells can be considered $B_{REG}$ cells. Some of these findings were corroborated in a murine cardiac transplantation model, in which marginal zone B-cell-derived IL-10 proved essential for induction of regulatory $T_{FH}$ cells and tolerance toward the allograft [28].

## DIFFERENT SUBSETS OF REGULATORY B CELLS

A number of different human and murine $B_{REG}$ cells have been identified based on phenotypic and functional characteristics. It goes beyond the scope of this review to describe all $B_{REG}$ subsets in detail and comprehensive reviews on this topic have been published elsewhere [3,4]. In the mouse system, $B_{REG}$ cells are found among cells with a B1a-like cells (i.e. $CD5^+$ B cells) [29], among B cells with an immature/transitional phenotype [30,31], and among cells with a plasma cell phenotype [32]. In the human system, the major phenotypes of $B_{REG}$ cells are $CD27^+CD24^{hi}CD148^{hi}CD48^{hi}$ B10/pro-B10 cells [18], $CD24^{hi}CD38^{hi}$ immature B cells [20], $CD73^-CD25^+CD71^+$ type 1 regulatory B ($B_R1$) cells, and $CD27^{int}CD38^{+/hi}$ plasmablasts [3,17,32].

## REGULATORY B CELLS AND THEIR ROLE IN TOLERANCE INDUCTION TO ALLERGENS

The majority of studies on $B_{REG}$ cells have focused on their role in autoimmune diseases. However, an increasing body of evidence supports a potential role for $B_{REG}$ cells in maintaining and restoring tolerance to allergens. Several recent studies provide support for a role for $B_{REG}$s in AIT. Mechanisms through which $B_{REG}$s could support AIT include induction of $T_{REG}$ cells, direct suppression of effector T cells, indirect suppression of effector T cells through inhibition of Dendritic cell (DC)

maturation, and production of IgG4 antibodies. Studies focusing on mouse models of allergic disease, primarily demonstrated a role for $B_{REG}$ cells with a B1a-like phenotype [10,26,33], whereas human studies focused on allergic disease primarily reported on $B_R1$ cells [8,34▪,35].

## REGULATORY B CELLS IN INDUCTION AND MAINTENANCE OF TOLERANCE TO ALLERGENS IN HUMANS

The aim of AIT is typically to restore clinical and immunological tolerance to allergens [36]. This requires the alteration of a $T_H2$ and IgE-dominated allergic response toward a healthy immune response. Healthy immune responses to allergens have been studied primarily in cat owners and beekeepers. Hallmarks of a healthy response to allergens are induction of IL-10-producing inducible type 1 regulatory T ($T_R1$) cells and blocking IgG(4) antibodies [37].

A human $B_{REG}$ subset that has been studied in the context of tolerance to allergens are $CD73^-CD24^+CD71^+$ $B_R1$ cells [8]. These cells could efficiently suppress antigen-specific $CD4^+$ T-cells proliferation. Data supporting a role for human $B_{REG}$ cells in developing tolerance to allergens comes primarily from studies on bee venom allergic individuals and healthy beekeepers. B cells specific for the major bee venom allergen phospholipase A2 (PLA) were identified using fluorescently labelled PLA. The frequency of IL-10-producing B cells among these allergen-specific B cells showed a two to five-fold increase in bee venom allergic patients at 3–4 months after the start of venom immunotherapy (VIT). After this increase the frequency of PLA-specific IL-10-producing B cells was at a comparable level as in healthy beekeepers during the season [8]. It remains to be elucidated whether allergen-specific B cells upregulate IL-10 production during VIT, or preexisting IL-10-producing allergen-specific B cells proliferate during VIT. Apart from IL-10, allergen-specific B cells also upregulated C-C chemokine receptor (CCR)5, a receptor for Macrophage Inflammatory Protein 1α and β as well as regulated on activation, normal T cell expressed and secreted, during VIT [34▪]. Although CCR5 expressed on $T_{REG}$ cells has been found to mediate their migration to inflammatory sites [38], its function on allergen-specific $B_{REG}$ cells remains to be determined.

The frequency of circulating allergen-specific B cells has been shown to increase during peanut immunotherapy and VIT [34▪,39,40▪▪]. A fraction of these cells may be $IL\text{-}10^+$ allergen-specific B cells [8]. In accordance with increases in serum levels of allergen specific IgG4 of that are frequently observed during AIT [36], it was primarily expansion of allergen-specific IgG4-switched B cells that drove this increase of allergen-specific B cells during VIT [34▪]. Increases in specific IgG4 during AIT correlate with clinical outcome in some, but not all studies [36]. One intriguing possibility is that not just an increase of specific IgG4 is sufficient for clinical improvement but rather the generation of high-affinity-specific IgG4 antibodies. This concept is technically challenging to prove, but recent work indicates that IgG4 (but not IgE)-switched peanut allergen-specific B cells accumulate an increasing proportion of more highly mutated sequences over time during the course of peanut oral immunotherapy [40▪▪]. As increased levels of somatic mutations are indicative of affinity maturation [41], these data suggest that IgG4 antibodies increase their affinity during AIT.

Very interesting in the context of a potential role for $B_{REG}$ cells during AIT is the link between IL-10-producing $B_R1$ cells and IgG4 production. Purified IL-10-producing B cells produced significantly increased levels of IgG4 antibodies compared to $IL\text{-}10^-$ B cells, whereas other immunoglobulin isotypes were produced in comparable amounts by $IL\text{-}10^+$ and $IL\text{-}10^-$ cells [8]. Thus, $B_R1$ may promote allergen tolerence during AIT through IL-10-mediated suppressive effects and through directing the humoral response toward IgG4.

## REGULATORY B CELLS IN MOUSE MODELS OF TOLERANCE INDUCTION IN ALLERGIC AIRWAY INFLAMMATION

B cells can induce allergen tolerance through production of TGF-β as was demonstrated in an ovalbumin (OVA)-induced airway inflammation and tolerance model. Mice that were administered a short-term (7 day) daily intranasal OVA exposure developed sensitization, whereas chronically exposed mice (42-day exposure) developed tolerance. Adoptively transferred B cells isolated from hilar lymph nodes of chronically exposed mice suppressed allergic airway inflammation in sensitized recipient mice. This suppressive effect was independent of IL-10, as B cells isolated from tolerant $IL\text{-}10^{-/-}$ mice exerted similar suppressive capacity [42]. Later it was found that $CD5^+CD1d^{hi}$ B cells were expanded in hilar lymph nodes of tolerant mice. These cells produced TGF-β and induced FoxP3 expression in $CD4^+$ T cells *in vitro* and suppressed development of allergic airway inflammation *in vivo* via enhanced accumulation of $Foxp3^+$ T cells in the lung [24].

A recent study with a different approach demonstrated that development of OVA-induced airway

inflammation and tolerance induction were developed similarly in wild-type (WT) and B cell-deficient (μMT) mice, indicating that B cells are not required for establishing OVA-induced airway inflammation. Tolerance could be induced by pretreatment with a high dose of intranasally administered OVA both in WT and μMT mice, suggesting that B cells were dispensable for tolerance induction in this model. IL-10 production by purified splenic B cells in response to lipopolysaccharide stimulation from OVA-sensitized and tolerized showed a similar and modest increase compared with control mice [25]. The effect of TGF-β production was not assessed in this study. It is interesting to note here that OVA-induced airway inflammation was accompanied by elevated germinal centre B cells numbers and elevated specific immunoglobulin production, whereas these B cell alterations were attenuated upon tolerance induction. Moreover, marginal zone precursor B cells from tolerant mice could induce $T_{REG}$ cells *in vitro* [25].

Methodological differences (e.g. application routes, dosing schemes, B cell-deficient mice vs. adoptive transfer experiments) may partially explain the seemingly different conclusions of these studies. However, taken together these datapoint out that in high-dose OVA tolerance induction models for allergic airway inflammation, $B_{REG}$ cells can be induced or expanded. These $B_{REG}$ cells have the capacity to induce $T_{REG}$ cells and, upon adoptive transfer, confer allergen tolerance in sensitized recipient mice in an IL-10-independent manner. TGF-β could be the driving factor in this process. These $B_{REG}$ cells may therefore contribute to allergen-tolerance induction in such an AIT model but the fact that B cell-deficient mice still develop tolerance indicates that there is redundancy with other suppressor cells.

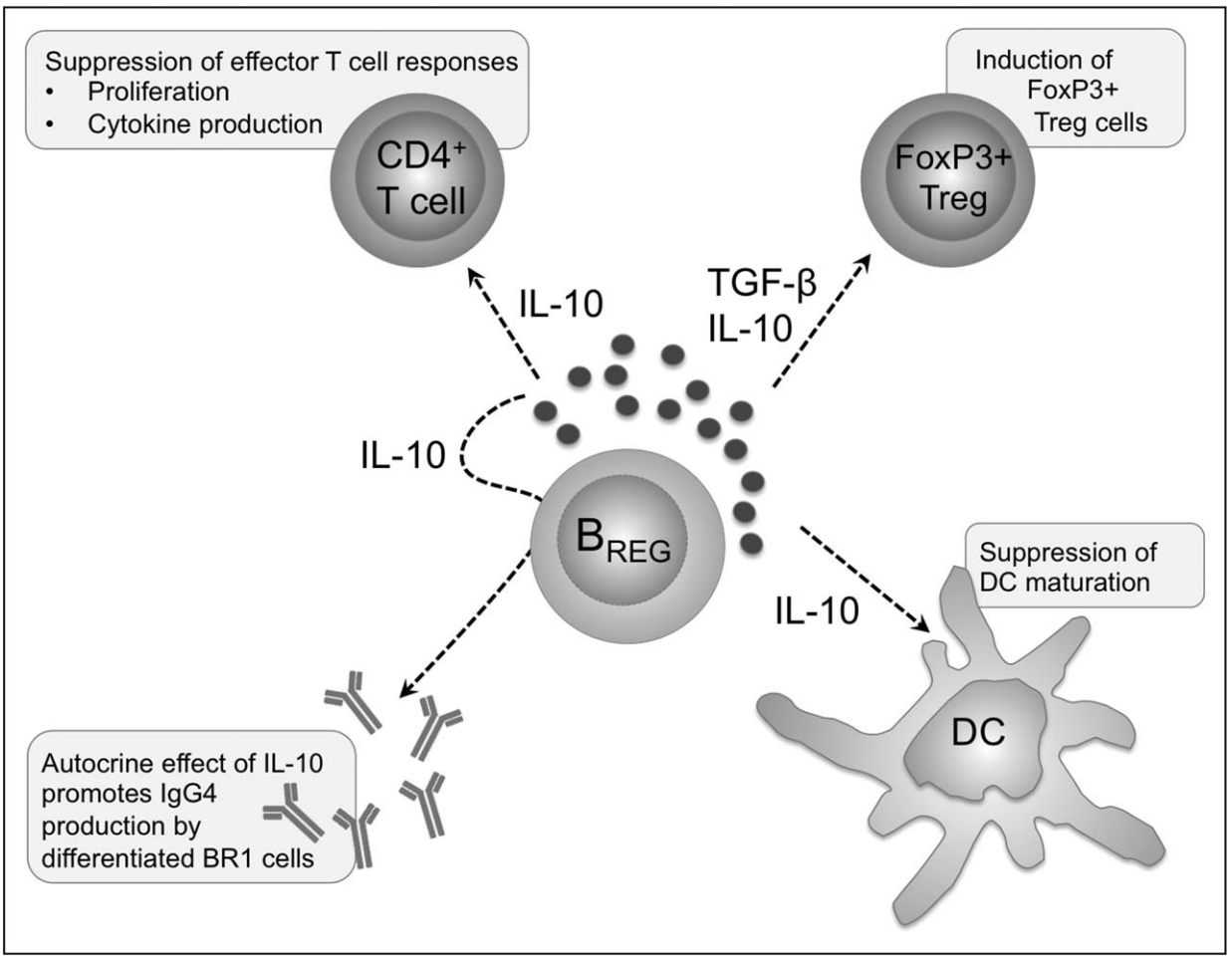


**FIGURE 1.** Mechanisms of $B_{REG}$-mediated immunoregulatioin during AIT. IL-10 and TGF-β can be produced by $B_{REG}$ cells. IL-10 can suppress effector T-cell responses directly but also indirectly through suppression of DC maturation. IL-10 produced by $B_{REG}$ cells may promote IgG4 production in an autocrine, as well as a paracrine manner. Both $B_{REG}$ cells can induce $T_{REG}$ cells through IL-10 and TGF-β. AIT, allergen immunotherapy; $B_{REG}$, regulatory B; TGF, transforming growth factor.

## REGULATORY B CELLS IN MOUSE MODELS OF TOLERANCE INDUCTION IN ALLERGIC INTESTINAL INFLAMMATION

Similar to what was found in models of allergic airway inflammation, B-cell-derived TGF-β may play a key role in tolerance induction to food allergens. A fraction of $CD5^+CX3CR1^+$ B cells present in the intestine of naive Bagg albino mice produced TGF-β in response to stimulation with αvβ6 and a B cell receptor (BCR) crosslinking antibody. Intestinal epithelial cells may recruit $CD5^+CX3CR1^+$ B cells, through production of fractalkine, which is a ligand for CXCR3. Food antigen-specific $CD5^+CX3CR1^+$ B cells could form a local source of TGF-β upon encounter of their cognate antigen and epithelial cell-derived αvβ6. Adoptive transfer of $CD5^+CX3CR1^+$ B cells could ameliorate $T_H2$-mediated intestinal inflammation [26]. A factor that may promote TGF-β production by B cells is thrombospondin 1, which enhances generation of active TGF-β. When mice sensitized with OVA and cholera toxin (to induce intestinal inflammation) received an AIT regimen in the form of increasing doses of gavage-fed OVA, $CD35^+$ B cells in the lamina propria increased in frequency and produced thrombospondin 1 [43].

## CONCLUSION

AIT has been used with considerable success for over a century. Increasingly detailed knowledge has been accumulated on the immunological mechanisms that drive successful clinical outcome of this therapy. $B_{REG}$ cells have only recently been identified as potentially relevant cells in the induction and maintenance of allergen tolerance. Currently available data suggest potential roles for $B_{REG}$ cells in AIT treatment of allergic airway inflammation, food allergies, and venom allergies. Mechanisms through which $B_{REG}$ cells may contribute to tolerance induction during AIT are summarized in Fig. 1 and include IL-10-mediated suppression of effector T cell, including $T_H2$ responses [8,26], induction of $T_{REG}$ cells [24,25], IL-10-mediated inhibition of DC maturation [44], modulation of $T_{FH}$ responses [27▪,28], and production of anti-inflammatory IgG4 antibodies [8,34▪]. A better understanding of the role of B cells and $B_{REG}$ cells in AIT could open up potential windows for developing targeted therapies specifically focused on promoting $B_{REG}$ responses during AIT.

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### Conflicts of interest

*There are no conflicts of interest.*

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- ▪ of special interest
- ▪▪ of outstanding interest

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